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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,993	02/27/2004	David J. Madar	6979USP1	7391

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EXAMINER

SHIAO, REI TSANG

ART UNIT	PAPER NUMBER
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1626

DATE MAILED: 08/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/788,993

Applicant(s)

MADAR ET AL.

Examiner

Robert Shiao

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) 25-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 12/05/05, 6/14/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. This application claims benefit of the provisional application:
60/412,084 with a filing date 09/19/2002.
2. Claims 1-30 are pending in the application.

Information Disclosure Statement

3. Applicant's Information Disclosure Statements, filed on December 05, 2004 and June 14, 2004, have been considered. Please refer to Applicant's copies of the 1449's submitted herein.

Responses to Election/Restriction

4. Applicant's election with traverse without arguments of Group II claims 1-24, in part, in the reply filed on June 02, 2006, is acknowledged.

Claims 1-30 are pending in the application. The scope of the invention of the elected subject matter is as follows.

Claims 1-24, in part, drawn to a compound of the formula (I), wherein the variable X is as defined in claim 1; the variable R does not represent heterocyclecarbonyl, (1, 2,3)-dioxoborolane or 4,4,5,5-tetramethyl- (1, 2,3)-dioxoborolane thereof; the variable R₁ does not represent heterocycle, heterocyclealkyl, or heteroaryl thereof, the variable R₁ is not substituted with heterocycle, heterocyclealkyl, or heteroaryl thereof; the heterocycle of variables R₂ or R₃ independently represent pyrimidine, pyridinyl, or piperidine thereof; variables R₂ and R₃ taken together with the atom to which they are attached do not form a mono or bicyclic heterocycle thereof.

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Claims 1-24, in part, embraced in above elected subject matter, are prosecuted in the case. Claims 1-24, in part, not embraced in above elected subject matter, and claims 25-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The requirement is still deemed proper.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutically acceptable salts of the compounds of the formula (I), does not reasonably provide enablement for prodrugs of the compounds of the formula (I), see claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

The nature of the invention is the compounds of the formula (I), their prodrugs or pharmaceutically acceptable salts thereof.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that prodrugs are inactive substances that are converted to a drug within the body by enzymes or other chemicals. Prodrugs can be formed by various mechanisms and vary depending on the functional groups present in the parent compound, i.e. different prodrugs would arise from parent compounds containing varying functional groups, such as a carboxylic acid, ester, an alcohol or an amine, all of which would require differing mechanism.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the

compounds of the formula (I) and their pharmaceutically acceptable salts of the compounds. There is no data present in the instant specification for the preparation of constitutional prodrugs of the instant compounds of the formula (I).

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically, the instant claims include any prodrugs, i.e. any compound of formula (I) with various functional groups, no matter what the chain length and any covalently bonded compound that would release the active parent compound.

The quantity or experimentation needed and the level of skill in the art

While the level of the skill in the pharmaceutical arts is high, it would require undue experimentation of one of ordinary skill in the art to prepare any prodrug of the formula (I) as instantly claimed since a prodrug of the compounds of the formula (I) can have varying functional groups in varying positions. It would also require undue experimentation to prepare any covalently bonded compound that would release the active parent drug since prodrugs are formed by varying mechanisms and depend on the functional groups of the parent compound. The only guidance present in the instant specification is for the compounds of the formula (I) and their pharmaceutically acceptable salts thereof. There is no guidance or working examples present for constitutional prodrugs of the formula (I). Applicant's statement regarding prodrugs is that any prodrug of the compound of formula (I) are rapidly transformed *in vivo* to the parent compounds, for example, by hydrolysis in blood, see page 28, lines 14-20.

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Therefore, the claims lack enablement for all prodrugs of the compounds of the formula

(I). Dependent claims 2-24 are also rejected along with claim 1 under 35 U.S.C. 112, first paragraph. This rejection can be overcome by deleting the limitation "prodrugs" from the instant claims.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

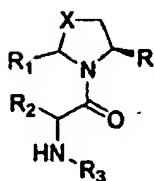
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Villhauer's US 6,011,155.

Applicants claim a pyrrolidine compound of the formula (I) as a DPP-IV inhibitor, i.e.,

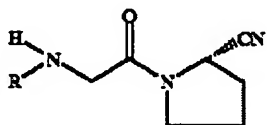


, wherein the variable X represents CH₂, and the variable R represents cyano, and the variable R₂ and R₃ independently represents hydrogen, alkyl, cycloalkyl, aryl or heterocycle (i.e., piperidine), the variable R₁ represents alkyl, see claim 1. Dependent claims 2-24 further limit a number of variables, i.e., R is cyano.

Determination of the scope and content of the prior art (MPEP §2141.01)

Vilhauer discloses a N-(substituted glycyI)-2-cyanopyrrolidine compound of formula I as a DPP-IV inhibitor,

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, wherein R is (C₃₋₁₂)cycloalkyl or piperidine, see columns

1-2.

Determination of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant product and Villhauer's compounds is that R₁ of instant claims represents alkyl (i.e., methyl), while Villhauer's is hydrogen.

Finding of prima facie obviousness-rational and motivation (MPEP §2142-2143)

One having ordinary skill in the art would find the claims 1-24 prima facie obvious because one would be motivated to employ the compounds of Villhauer's to obtain the instant compounds of formula (I), wherein the variable X represents CH₂, and the variable R represents cyano, and the variable R₂ and R₃ independently represents hydrogen, alkyl, cycloalkyl, aryl or heterocycle (i.e., piperidine), the variable R₁ represents alkyl (i.e., methyl). It is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results, see *In re Wood*, 199 U.S.P.Q. 137 (C.C.P.A. 1978) and *In re Lohr*, 137 U.S.P.Q. 548, 549 (C.C.P.A. 1963). Dependent claims 2-24 are also rejected along with claim 1 under 35 U.S.C. 103(a) as the same reasons described above.

The motivation to make the claimed compounds derives from the expectation that the instant claimed compounds derived from Villhauer's known compounds would

possess similar activity (i.e., DPP-IV inhibition activity) to that which is claimed in the reference.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

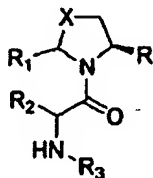
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of Madar et al. co-pending application No. 11/036,258, see US 2005/0215784 A1. Although the conflicting claims are not identical, they are not patentably distinct from

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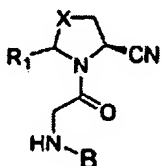
each other and reasons are as follows.

Applicants claim a pyrrolidine compound of the formula (I) as a DPP-IV inhibitor, i.e.,



, wherein the variable X represents CH₂, and the variable R represents cyano or arylcarbonyl, and the variable R₂ and R₃ independently represents hydrogen, alkyl, cycloalkyl, aryl or heterocycle (i.e., pyridinyl, piperidine or piperidinyl), the variable R₁ represents alkynyl or cyano, see claim 1. Dependent claims 2-24 further limit a number of variables, i.e., R is cyano.

Madar et al. claim a pyrrolidine compound of the formula (II) as a DPP-IV



inhibitor, i.e., , wherein the variable X represents CH₂, the variable B represents piperidinyl or pyridinyl, the variable R₁ represents alkynyl or cyano.

The difference between the instant claims and Madar et al. is that the instant variable R₃ represents hydrogen, alkyl, cycloalkyl, aryl or heterocycle (i.e., pyridinyl, piperidine or piperidinyl), while Madar et al. represents piperidinyl, pyridinyl, dioxanyl, furyl, or imidazolyl at the same position.

One having ordinary skill in the art would find the instant claims 1-24 prima facie obvious **because** one would be motivated to employ the compounds of

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Madar et al. to obtain the instant compounds of formula (I), wherein the variable X represents CH₂, and the variable R represents cyano or arylcarbonyl, and the variable R₂ and R₃ independently represents hydrogen, alkyl, cycloalkyl, aryl or heterocycle (i.e., pyridinyl, piperidine or piperidinyl), the variable R₁ represents alkynyl or cyano.

Dependent claims 2-24 are also provisional rejected along with claim 1 under the obviousness-type double patenting.

The motivation to obtain the claimed compounds of formula (I) derives from known Madar et al. compounds would possess similar activities (i.e., DPP-IV inhibitors) to that which is claimed in the reference.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

10. Claims 1-24 are objected to as containing non-elected subject matter, i.e., heterocycle, (1, 2,3)-dioxoborolane or 4,4,5,5-tetramethyl- (1, 2,3)-dioxoborolane, piperazine, morpholine, furyl, or 2-quinolinyl, etc. It is suggested that applicants amend the claims to the scope of the elected subject matter as defined on the pages 2-3 *supra*.

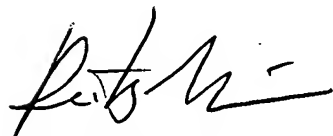
11. Claims 6, 10, 12, 16, 18, 20, 22, and 24 are objected. It appears there is a typographic error of the last second compound of each claim, insertion of a term "and" after the name of the last second compound respectively would obviate the objection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Robert Shiao, Ph.D.
Patent Examiner
Art Unit 1626

July 26, 2006